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Temporal Variations in Trough Serum Theophylline Concentrations at Steady State

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Abstract □ Temporal variations in serum theophylline concentrations were observed in 14 healthy volunteers receiving multiple doses of theophylline. After repeated oral doses (6.9–18.2 mg/kg/day) of theophylline as either a nonalcoholic aminophylline solution or a controlled-release capsule, trough theophylline levels at steady state were significantly higher ($p < 0.05$) in the morning than in the afternoon or evening. With the solution, the mean ($\pm SE$) trough serum level at 7 am was 11.1 ± 0.9 μg/ml, and at 1 pm it was 9.6 ± 0.8 μg/ml. With the capsule, the mean ($\pm SE$) trough serum level at 8 am was 13.8 ± 0.9 μg/ml, and at 8 pm it was 10.7 ± 0.9 μg/ml. Temporal variations in serum theophylline concentrations have not been reported previously and may be important in therapeutic monitoring.

Keyphrases □ Theophylline—trough serum concentrations at steady state, temporal variations □ Bronchodilators—theophylline, trough serum concentrations at steady state, temporal variations □ Pharmacokinetics—theophylline, trough serum concentrations at steady state, temporal variations

Temporal variation in the absorption and disposition of drugs is an area of pharmacokinetics about which relatively little is known. In the few studies performed, the findings have not been consistent. For example, Shirley and Vesell (1) reported that temporal variations in the disposition of acetaminophen and phenacetin occur. However, Vesell *et al.* (2) observed no temporal variations in the pharmacokinetics of antipyrine (2), and Nakano and Hollister (3) reported no time-related changes in the disposition of nortriptyline. The causes of temporal variations in drug pharmacokinetics may be varied. Circadian rhythm apparently influences the distribution of potassium between body compartments (4), while changes in body posture alter the absorption of cephradine (5) and erythromycin (6) from the GI tract.

One mechanism suggested to account for the temporal variations in the disposition of phenacetin and acetaminophen was the occurrence of diurnal changes in the amount and activity of hepatic microsomal oxidases (1). Theophylline is a drug whose disposition also is determined by microsomal oxidases, so it seemed possible that temporal variations in theophylline disposition may occur. Since this aspect of theophylline kinetics had not been reported previously, one objective of this study was to determine if temporal variations exist.

EXPERIMENTAL

Subjects—The seven male and seven female volunteers were 21–40 years old, and their average weight was 67.5 kg. All volunteers were nonsmokers and were in good physical health with no history of alcoholism or cardiovascular disease.

Drug Administration and Blood Sampling—The volunteers randomly received either a nonalcoholic aminophylline solution or a controlled-release theophylline capsule. The oral theophylline dose was individualized for each volunteer, based on single-dose kinetics, to produce peak serum theophylline concentrations no larger than 18 μg/ml after repeated dosing. The daily doses ranged from 6.9 to 18.2 mg/kg. The solution was administered at 7 am, 1 pm, 7 pm, and 1 am, and the capsule was given at 8 am and 8 pm. Dosing was continued for 6 days prior to each study day. The study days were separated by 1 week during which the volunteers took the alternate formulation.

On each study day, 1 ml of serum was obtained immediately before the morning dose of each dosage form and 6 or 12 hr after administration of the solution or capsule, respectively.

Theophylline Assay—Serum theophylline determinations were made by high-pressure liquid chromatography using a method described previously (7).

Data Analysis—A paired t test was used to analyze within-subject differences between the am and pm trough theophylline concentrations observed for each dosage form.

RESULTS AND DISCUSSION

The am and pm trough serum theophylline concentrations determined for each dosage form are listed in Table I. The percentage changes in trough level are noted for each volunteer. The mean ($\pm SE$) serum theophylline concentration at 7 am for the solution was 11.1 ± 0.9 μg/ml, while at 1 pm the serum theophylline concentration was 9.6 ± 0.8 μg/ml, representing a change of 13%. For the capsule, the mean ($\pm SE$) serum theophylline concentration at 8 am was 13.8 ± 0.9 μg/ml, and at 8 pm it was 10.7 ± 0.9 μg/ml, reflecting a decrease of 24%. The differences between the am and pm serum theophylline concentrations were significant ($p < 0.05$) for each dosage form.

Based on these results, there appear to be temporal variations in theophylline pharmacokinetics. Higher trough levels at 7 or 8 am compared to those at 1 or 8 pm may be related to a shorter plasma half-life at the latter times. Indeed, Shirley and Vesell (1) reported that plasma half-lives of phenacetin and acetaminophen were ~15% shorter at 2 pm than at 6 am. Another possible cause of higher am trough levels may be

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Table I—Trough Serum Theophylline Levels (Micrograms per Milliliter) in 14 Subjects after Administration of Either a Nonalcoholic Aminophylline Solution or a Controlled-Release Theophylline Capsule

Subject	Daily Dose, mg/kg	Solution			Capsule		
		7 am	1 pm	% Chg[a]	8 am	8 pm	% Chg[a]
A	8.1	6.6	5.0	24.2	6.1	4.1	32.8
B	18.2	14.1	12.7	9.9	16.3	13.8	15.3
C	18.0	7.4	6.0	18.9	15.0	9.1	39.3
D	6.9	7.0	6.6	5.7	12.0	7.3	43.0
E	11.1	14.0	13.0	7.1	17.1	13.1	23.3
F	16.2	15.0	12.0	20.0	15.7	12.7	19.1
G	14.5	14.2	12.4	12.7	16.5	13.2	20.0
H	12.0	14.4	11.5	13.2	14.4	13.4	6.9
I	8.0	8.0	6.5	18.8	11.7	6.3	46.2
J	11.5	14.6	13.6	6.8	13.3	10.8	18.8
K	14.3	11.3	9.7	14.2	13.8	10.4	24.6
L	9.4	7.7	6.1	20.8	8.1	6.2	23.5
M	9.2	11.6	11.6	0.0	13.9	13.2	6.0
N	16.1	8.9	8.3	6.7	18.5	15.7	15.1
Mean		11.1	9.6	12.8	13.8	10.7	23.8
±*SEM*		0.9	0.8	1.9	0.9	0.9	3.4

[a] Percent decrease in trough level from the am to pm period.

slower absorption of the nighttime dose. Nakano and Hollister (3) reported that nortriptyline was absorbed slower after an evening oral dose than after a morning dose. In this study of theophylline, the volunteers were primarily in the supine position after the 1-am and 8-pm doses, which may have slowed absorption. The supine position has been shown to account for slowed absorption of cephradine (5) and erythromycin (6).

Since serum level determinations are widely used to monitor theophylline therapy, temporal variations in theophylline kinetics may be important in the clinical setting. The results emphasize the importance of timing in therapeutic drug monitoring. Serum theophylline concentrations vary with time during a dosage interval at steady state and, based on this study, from one dosage interval to the next. In monitoring theophylline therapy from 1 day to another, it is important to obtain a trough serum theophylline concentration at the same time on each day.

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